

## REMARKS

This is intended as a full and complete response to the Office Action dated December 15, 2004, having a shortened statutory period for response set to expire on March 15, 2005. Please reconsider claims 1-37 pending in the application for reasons discussed below.

### ***Claim Rejections - 35 U.S.C. § 103***

Claims 1-4, 6-15 and 22-24 stand rejected under 35 U.S.C. § 103 as being unpatentable over *Villanueva, et al.* (WO 99/13918) in view of *Averkiou, et al.* (U.S. Patent No. 6,171,246). Applicants respectfully traverse the rejection.

*Villanueva, et al.* teaches that microbubbles must be conjugated to a molecule having binding affinity for ICAM-1 in order to “permit for the first time (emphasis added) the visualization of microbubbles adherent to activated coronary endothelial cells *in situ*.” *Averkiou, et al.* teaches that blood flow can be imaged using microbubbles at a mechanical index of 0.1 or less. However, there is no teaching to replace imaging disclosed in *Villanueva, et al.* performed at energy ranges insufficient to rupture the microbubbles with low mechanical index imaging taught in *Averkiou, et al.*, as suggested by the Examiner. In addition, *Averkiou, et al.* only teaches imaging or measuring blood flow and not retention of the microbubbles in the vessel and subsequently identifying dysfunction of the vessel at that location. Accordingly, the Examiner has merely indicated that the references can be combined or modified without showing that the prior art suggests the combination.

In contrast, the present invention utilizes a low mechanical index pulse sequence which enables viewing of microbubbles without requiring specialized antibodies or ligands for endothelial cells. Furthermore, it is only the present invention that describes the desirability of using low mechanical index imaging to detect retention of the microbubbles in a vessel to indicate dysfunctional vascular endothelium “since the number of microbubbles that adhere to dysfunctional endothelial cells is small, this higher sensitivity/low mechanical index pulse sequence scheme is ideal for non-invasive

characterization of the physiologic features of the endothelium.” (See, paragraph [0042]) Therefore, there is no motivation or suggestion to combine the references to produce the claimed invention without improper hindsight.

For the foregoing reasons, *Villanueva, et al.* in view of *Averkiou, et al.* fails to teach, show or suggest performing transcutaneous imaging of a vessel of interest using a low mechanical index pulse sequence, wherein the retention of microbubbles in the vessel indicates dysfunctional vascular endothelium, as recited in claim 1. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of claim 1 and claims 2-4, 6-15 and 22-24 dependent thereon.

Claim 5 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over a combination of *Villanueva, et al.* and *Porter, et al.* as applied to claim 4 and in view of *Widlansky, et al.* (JACC 10/2003).

It appears the Examiner intended to cite *Averkiou, et al.* instead of *Porter, et al.* in the rejection of claim 5 since the Examiner indicated that claim 4 was not patentable over the combination of *Villanueva, et al.* with *Averkiou, et al.* and not *Villanueva, et al.* with *Porter, et al.* Regardless, *Porter, et al.* and/or *Widlansky, et al.* fail to overcome the deficiencies discussed above relating to *Averkiou, et al.* and *Villanueva, et al.* Specifically, *Porter, et al.* and *Widlansky, et al.* are both completely silent regarding low mechanical index imaging and retention of microbubbles in a vessel and subsequently identifying dysfunction of the vessel at that location. Therefore, claim 5 which is dependent on claim 1 is patentable over the cited references. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of this claim.

Claims 16-21 and 26-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over a combination of *Villanueva, et al.* and *Averkiou, et al.* in view of *Porter, et al.* (U.S. Patent No. 5,567,415). The Examiner states that it would have been obvious in view of *Porter, et al.* to use a sugar solution with the combination of *Villanueva, et al.* and *Averkiou, et al.* as set forth above. Applicants respectfully traverse the rejection.

As discussed above with respect to the rejection of claims 1-4, 6-15 and 22-24, Applicants submit that there is no motivation or suggestion to modify *Villanueva, et al.* with *Averkiou, et al.* Further, *Porter, et al.* fails to remedy the deficiency of *Villanueva,*

*et al.* relating to the mechanical index used or the shortage of *Averkiou, et al.* regarding retention of microbubbles to detect dysfunction since the Examiner only relies on *Porter, et al.* for teaching use of a sugar solution. Therefore, *Villanueva, et al.* and *Averkiou, et al.* in view of *Porter, et al.* fails to teach, show or suggest performing transcutaneous imaging of a vessel of interest using a low mechanical index pulse sequence or a pulse sequence with a mechanical index of about 0.03 to about 0.4, wherein the retention of microbubbles in the vessel indicates dysfunctional vascular endothelium, as required by claims 16-21 and 26-36. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of these claims.

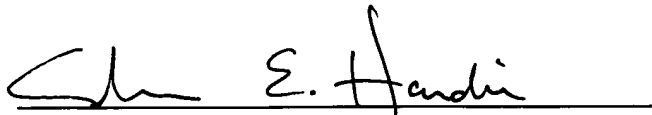
Claim 25 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over a combination of *Villanueva, et al.* and *Averkiou, et al.* in view of *Holley, et al.* (U.S. Patent No. 6,626,831). Claim 37 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over a combination of *Villanueva, et al.*, *Averkiou, et al.* and *Porter, et al.* in view of *Holley, et al.*

As described above in the traversals regarding independent claims 1 and 26 from which claims 25 and 37 depend, respectively, *Villanueva, et al.*, *Averkiou, et al.* and *Porter, et al.* fail to teach, show or suggest performing transcutaneous imaging of a vessel of interest using a low mechanical index pulse sequence or a pulse sequence with a mechanical index of about 0.03 to about 0.4, wherein the retention of microbubbles in the vessel indicates dysfunctional vascular endothelium. Further, *Holley, et al.* fails to overcome these deficiencies since *Holley, et al.* is completely silent regarding low mechanical index imaging and retention of microbubbles in a vessel and subsequently identifying dysfunction of the vessel at that location. Therefore, claims 25 and 37 are patentable over the cited references. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of these claims.

***Conclusion***

The references cited by the Examiner, alone or in combination, do not teach, show, or suggest the invention as claimed. Having addressed all issues set out in the office action, Applicants respectfully submit that the claims are in condition for allowance and respectfully request that the claims be allowed.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "C. E. Hardie", is written over a horizontal line.

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